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A dose-seeking trial of edatrexate in combination with vinblastin adriamycin, cisplatin, and filgrastim (EVAC/G-CSF) in patients advanced malignancies: promising antineoplastic activity agains non-small cell lung carcinomas.

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PURPOSE: To determine the maximum tolerated dose, toxicities, and potent antitumor activity of edatrexate (E), an antifolate agent with enhanced in vitr antitumor activity as compared with methotrexate (M), when given in combi with vinblastine, doxorubicin, cisplatin, and filgrastim (G-CSF) to patients w advanced malignancies. PATIENTS AND METHODS: Thirty-seven patient advanced malignancies were treated with escalating doses of edatrexate in combination with vinblastine (V), doxorubicin (A), cisplatin (C), and filgrast (EVAC/G-CSF) following three different subsequently developed schedules. Schedule 1 was patterned after the MVAC regimen, a combination chemothe program with activity against different epithelial malignancies, and consisted 40 mg/m2/day, days 1/15/22; V, 3 mg/m2/day, days 2/15/22; A, 30 mg/m2/ c day 2; C, 70 mg/m2/day, day 2; repeated every 28 days. Schedules 2 and 3 w designed to avoid observed dose-limiting toxicity on schedule 1 consisting o transient elevation of serum creatinine levels and delayed myelosuppression. Schedule 2 consisted of E, 40 or 60 mg/ m2/day, days 1 and 15; V, 3 mg/m2/ days 2 and 15; A, 30 mg/m2/day, day 2; C, 30 mg/m2/day, days 1 and 2; cyc every 28 days. Schedule 3 consisted of E, 60 to 120 mg/m2/day, day 1; V, 3 mg/m2/day, day 2; A, 30 mg/m2/day, day 2; C, 30 mg/m2/day, days 1 and 2; cycled every 21 days. Filgrastim 5 micrograms/kg/day was given to all patie subcutaneously until the absolute neutrophil count was greater than 10,000/m postnadir. Three patients were treated on schedule 1, 10 on schedule 2 (four a dose of 40 mg/m2/day and six at an E dose of 60 mg/m2/day), and 24 on sch 3 (six at each of the following E dosages: 60, 80, 100, and 120 mg/m2/day). RESULTS: Dose-limiting toxicities of grade 3 to 4 leukopenia and transient elevation of serum creatinine values were observed in two of three patients tr on schedule 1. A dose-limiting toxicity of grade 3 to 4 leukopenia was noted of six patients treated on schedule 2 at an edatrexate dose of 60 mg/m2/day.

of six patients treated on schedule 3 at an edatrexate dose of 120 mg/m2/day dose-limiting toxicity of grade 3 stomatitis (one patient) and grade 3 cytopen (one patient). Nineteen of 37 patients with evaluable or measurable disease h response to treatment (response rate 51%, 95% confidence intervals = 35%-6 Nine of 15 patients with metastatic non-small cell lung cancer responded, including one complete remission (response rate 60%, confidence intervals = 85%). A median survival of 517 days (confidence interval = 163-808 days) a 1-year survival rate of 60% (confidence interval = 35%-85%) was seen in pa with advanced non-small cell lung cancer. CONCLUSIONS: The maximum tolerated dose and the recommended phase II dose of edatrexate is 100 mg/m when administered as part of the EVAC/G-CSF program following schedule Promising antineoplastic activity against non-small cell lung carcinomas was observed, and a phase II study is planned.

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